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HYPOTHALAMIC TEMPERATURES IN DOG AND MONKEY AND THERMOREGULATORY RESPONSES TO ENVIRONMENTAL FACTORS

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[Prepared under Contract No. AF 33(657)-7603
by
Harold T. Hammel
Donald C. Jackson
Johannes A. J. Stolwijk
James D. Hardy
The John B. Pierce Foundation of Connecticut, Inc.,
New Haven, Connecticut]

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FOREWORD

This study was initiated by the Biothermal Section of the Biophysics Branch, Biomedical Laboratory, 6570th Aerospace Medical Research Laboratories. The research was conducted by the John B. Pierce Foundation Laboratory of New Haven, Connecticut, under Contract AF 33(657)-7603. Dr. Harold T. Hammel, Head of the Physiology Division, was the principal investigator for the John B. Pierce Foundation Laboratory. The work was performed in support of Project No. 7222, "Biophysics of Flight," Task No. 722204 "Human Thermal Stress." Dr. A. T. Kissen, Biothermal Section, was the contract monitor for 6570th Aerospace Medical Research Laboratories. This investigation was also supported in part by Contract AF 33(616)-6306 with 6570th Aerospace Medical Laboratories and by Grants B-1508 and NB 08826-02 with the National Institutes of Neurological Disease and Blindness, Bethesda, Maryland. The research was started in October 1961 and completed in November 1962.

The experiments reported herein were conducted according to the "Principles of Laboratory Animal Care" established by the National Society for Medical Research.

ABSTRACT

The role of the hypothalamic and skin temperatures in controlling the thermal response of a resting animal was studied by measurements of (1) hypothalamic, rectal, ear skin and trunk skin temperatures on the resting dog and rhesus monkey (hypothalamic temperature only) in hot, neutral and cold environments; and (2) the thermal and metabolic responses of a dog while holding hypothalamus at approximately 38.7°C by means of six thermodes surrounding the hypothalamus and perfused with water. The results indicate that the parameters involved in temperature regulation must include more than skin and hypothalamic temperatures since an animal engaged in normal regulation would exhibit very different responses for the same hypothalamic temperature when exposed to different ambient temperatures or would exhibit the same responses at widely different hypothalamic temperatures at different times, depending on whether asleep or awake. The discussion of these results includes a hypothesis of a dependent set point which suggests that the set point for temperature regulation depends upon the skin temperature, extra-hypothalamic core temperatures, whether the animal is asleep or awake, and other factors.

PUBLICATION REVIEW

This technical documentary report has been reviewed and is approved.

Jos M Quashnock

JOS. M. QUASHNOCK
Colonel, USAF, MC
Chief, Biomedical Laboratory

INTRODUCTION

When imposing an external thermal stress upon a homoiothermic animal, it is difficult to determine whether the heat producing and conserving responses and the heat dissipating responses of the animal are due to thermal receptors located in the periphery or in the core of the animal or due to some combination of these two. Although careful measurements of the motor responses of an animal to its thermal environment are important, without simultaneous measurements of hypothalamic, core and skin temperatures they do not serve to answer questions concerning the internal thermal drives or the type of controller involved in temperature regulation.

The role of the hypothalamic, core and skin temperatures in controlling the thermal response of a resting dog and monkey was studied by two methods (ref. 1, 2).

A. Many measurements of hypothalamic, rectal, ear skin and trunk skin temperatures were made on the resting, fasting dog in its winter fur in hot, neutral, and cold environments while observations of respiration rate, shivering, and body position were made. Twenty-four hour measurements were also made of the hypothalamic temperature of the rhesus monkey restrained in a primate chair in hot, neutral, and cold environments.

B. A "thermal clamp" was placed on the hypothalamus of a resting, fasting dog to hold the temperature of the hypothalamus at approximately 38.7°C while the thermal and metabolic responses were measured when exposed to a wide range of environmental temperatures. The response of such an animal may be attributed to the extra-hypothalamic thermal receptors. Subsequently, any increment of response that followed upon removal of the thermal clamp may be attributed to the hypothalamic receptors alone.

The objective for this study was to obtain a quantitative relationship between hypothalamic and skin temperature and the thermoregulatory responses of the animal. This objective was based on the assumption that there is a unique thermal and metabolic response for each combination of skin and hypothalamic temperatures in the resting animal. The observations, however, did not seem to support this assumption. Therefore, we have concluded that (1) there are thermal receptors in the core outside the hypothalamus; and/or (2) the regulated temperature in the body, the temperature from which a displacement will elicit an appropriate response either to increase or decrease the body temperature, is influenced by such factors as food and feeding, sleep and degree of alertness, apprehension, body position, temperature to which the animal was acclimatized in animal quarters, etc. This is to say that the "set point" or "set temperature" could be dependent on factors which, heretofore, have not been considered.

METHODS

Thermodes were implanted around the hypothalamus of mongrel dogs. The thermodes served both as re-entrant tubes for measurement of the hypothalamic temperature by inserting a thermocouple to the bottom of the tube and for thermal stimulation of the hypothalamus by perfusing the thermodes with water. Two rows of thermodes, each 4 mm from the midline, were passed through sleeve guides (18-gauge stainless tubing 12 mm long) driven through the skin and skull when the animal was under general anesthesia and the head was held in a stereotaxic instrument, Figure 1 (ref. 3, 4).

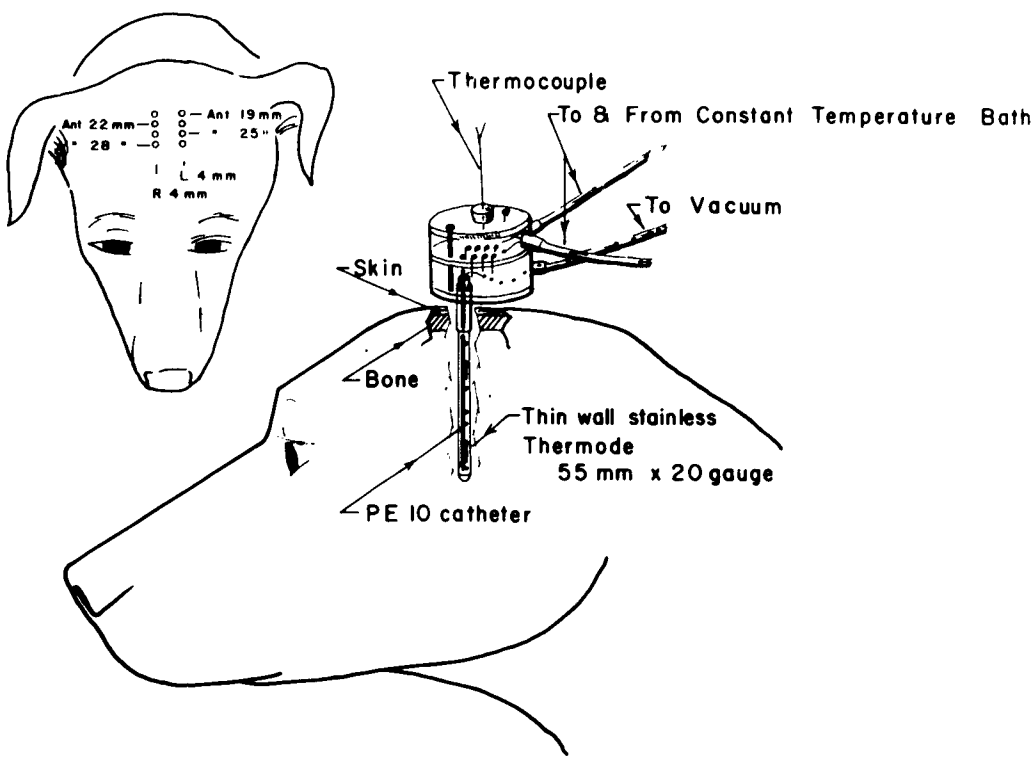

Fig. 1 Details of thermode (or re-entrant tube) and circulator construction. The circulator is shown in place for thermal stimulation of the hypothalamus. Only the lower acrylic plate or bottom of the circulator is left permanently attached to the thermodes and guides by epoxy resin.

The sleeve guides were placed in each row at 19, 22, 25 and 28 mm anterior to the ear bars. The anterior commissure in the dog is approximately 25 mm

anterior to the ear bars. The tops of the guides extended a few millimeters above the skin line. The thermodes were made of 20-gauge thin-wall stainless tubing, closed and rounded at the bottom end with a 0.5 mm hard solder plug and were approximately 55 mm long so that they extended to within 1 mm of the base of the cranium. Each thermode was electrically insulated with Formvar over its entire length except for a 4 mm section starting 1 mm from the bottom. The tops of all eight guides and thermodes passed up through an acrylic plate and were bonded to the plate with epoxy resin. During thermal stimulation, the acrylic plate became the bottom of a double chambered circulator. Several weeks after preparation, thermocouples were inserted into selected thermodes or the three anterior pairs were perfused with water from the circulator mounted above the head (Figure 1) and a thermocouple was placed in one of the posterior pair of thermodes. When thermal stimulation of the hypothalamus was required, water from a constant temperature bath was circulated through the upper chamber of the head circulator at a high rate. The bath temperature was held constant ($\pm$ 0.05°C), and the temperature could be quickly adjusted to any desired temperature between 30°C and 45°C by the addition of cold or hot water. The temperature of the water passing through the head circulator was continuously recorded with a thermocouple inserted in the upper chamber. Water from the upper chamber of the head circulator flowed to the tip of the thermode when the lower chamber was connected to a vacuum line.

The dog was trained to rest quietly on a platform in an air conditioned box, 35 x 29 x 29. Forced air entered the chamber through a 6-inch port in the top of the box above the dog. A baffle in front of the port prevented air from striking the dog directly. Air left the chamber through a 6-inch port low on one end of the chamber. The temperature of the box could be held constant at temperatures between 10°C and 45°C and rapid transitions could be made from one temperature to another.

Continuous recordings of oxygen consumption, evaporative heat loss from the mouth, rectal temperature, hypothalamic temperature, the average of 8 to 10 skin temperatures, the skin temperatures of the ear and trunk, air temperature and temperature of stimulating water were made as shown in Figure 2. The dog was trained to wear a clear, plastic hood over its head for metabolic measurements.

Rhesus monkeys were similarly prepared with thermodes (or re-entrant tubes depending on use) in two rows 3 mm to the left and 3 mm to the right of midline at 12.5 mm, 15.0 mm (level of the anterior commissure) and 17.5 mm anterior to the ear bars.

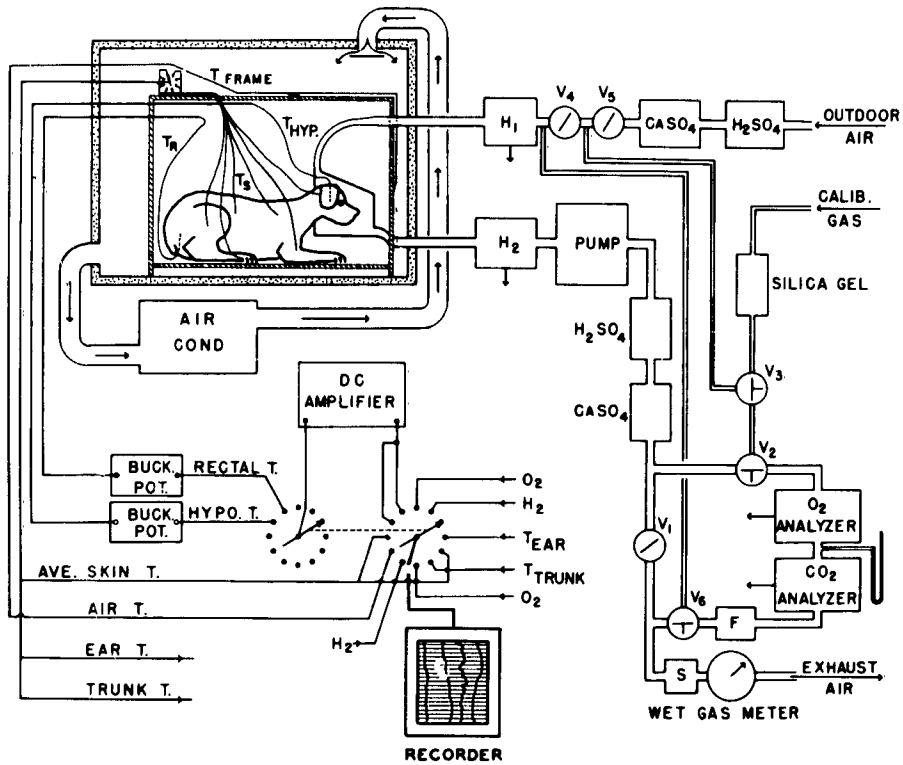

Fig. 2 System for recording oxygen consumption, evaporative heat loss from mouth, rectal, skin and hypothalamic temperatures, air temperature and temperature of stimulating water in head circulator.

RESULTS

A. Hypothalamic, Rectal, Ear Skin, and Trunk Skin Temperatures on Resting Dog Exposed to Hot, Neutral, and Cold Environments

Temperatures and notes on respiration rate and shivering are recorded in Figures 3, 4a, 4b, and 5 for three runs on separate days on the same dog. The dog still had its winter under-fur although living in heated animal quarters for two months. In the convective environment within the animal chamber, the neutral dry bulb temperature for this dog was about 25°C or 2° to 3°C below the neutral temperature for a dog without a winter coat of fur. For the first 33

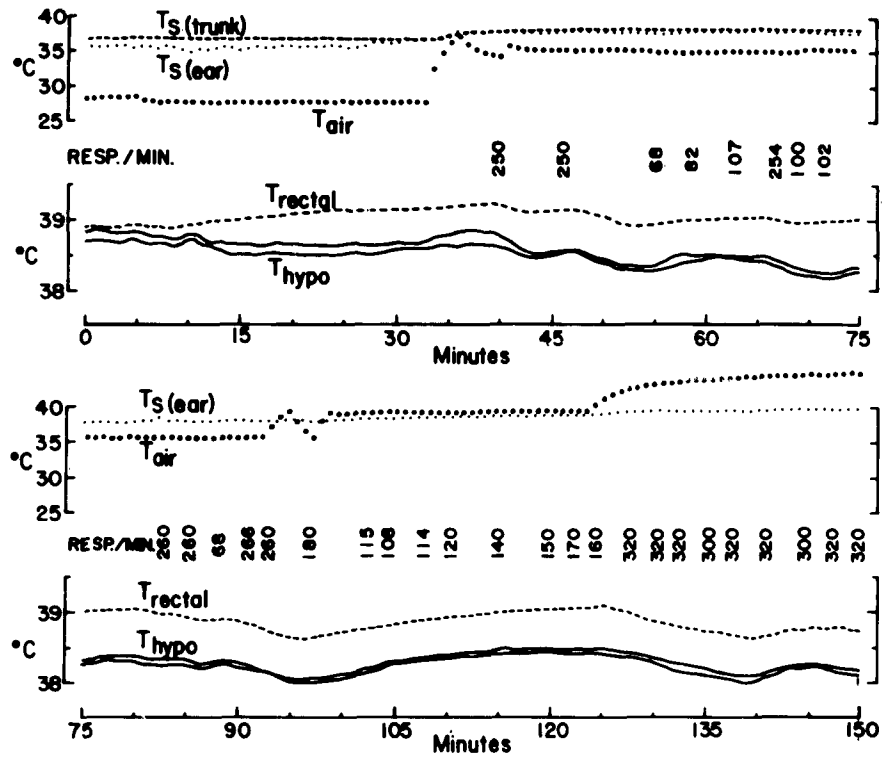

Fig. 3 Body temperatures of resting, fasting dog with winter fur exposed to warm and hot environments. T_s (trunk) = skin temperature of trunk; T_s (ear) = skin temperature of ear; T_{rectal} = rectal temperature; T_{hypo} = hypothalamic temperatures, upper solid line at Anterior 25 mm left 4 mm and lower solid line at Anterior 25 mm right 4 mm (see Figure 1); T_{air} = air temperature.

minutes of the record in Figure 3, the dog rests quietly at 27°C. (Note that the lower record is a continuation of the upper record.) The high ear temperature indicates that the animal was vasodilated. The air temperature was raised to 35°C which shortly thereafter initiated panting. With respiration rates in excess of 250 breaths per minute, the dog was usually able to lower its hypothalamic and rectal temperatures. At an air temperature above 45°C the dog, by panting, dropped its hypothalamic temperature from 38.5°C down to 38.1°C. Both hypothalamic temperatures in Figure 3 were recorded at the level of and below the anterior commissure.

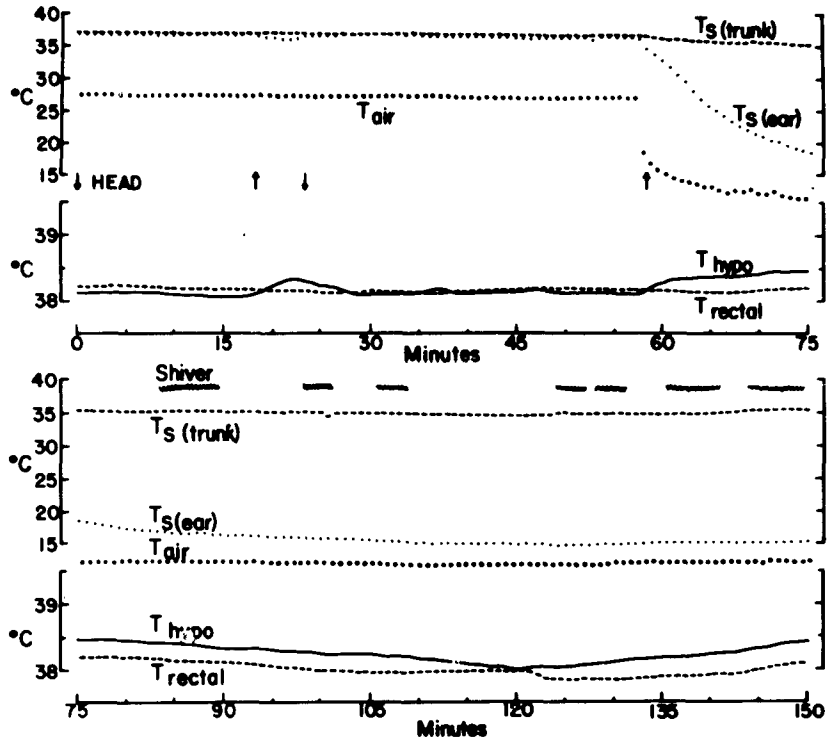

Fig. 4a Body temperatures of same dog as Fig. 3 resting and fasting exposed to neutral, cold, and hot environments.

In Figure 4a the dog was again started off in a warm environment of 27°C. Here is illustrated an event often seen in animals in neutral or warm environments (but not in cold). When the head was down, the hypothalamic temperature was lower than when the head was held up. The difference may be as much as 0.5°C and a decreasing temperature never elicits shivering nor does an increasing temperature elicit panting. The temperature of the hypothalamus is determined at all times by its rates of heat production and heat loss. The only time-dependent parameters affecting the temperature are heat production in, temperature of the blood entering, and rate of blood flow through the hypothalamus. The change in the hypothalamic temperature in Figure 4a was probably not due to changes in the arterial blood temperature, since the hypothalamic temperature was changing so rapidly and there was no concomitant change in rectal temperature. The changes in temperature might be partly explained by changes in the blood flow rate of the brain stem (ref. 5).

When the head was elevated, the perfusion pressure of the brain decreased by the amount of hydrostatic pressure of the column of blood from heart to head causing the blood flow to decrease so that the brain was cooled less. The falling hypothalamic temperature was, however, associated with drowsiness and sleep when the animal put its head down. Serota has suggested that the lowered brain temperature in the sleeping cat is due to a lower cell metabolism rather than to any marked change in blood flow, indicating that sleep is associated with a decreased rather than an increased activity of the hypothalamus (ref. 6).

At 58 minutes in Figure 4a, the air temperature was dropped from 27°C to 10°C. Within 30 minutes, traces of shivering occurred at a hypothalamic temperature of 38.5°C. The shivering was not vigorous enough to prevent a decline to 38.1°C. Note that in Figure 3, the animal was panting at no higher hypothalamic temperatures than these. The animal can shiver enough to regain hypothalamic temperature, as seen at 120 to 150 minutes in Figure 4a.

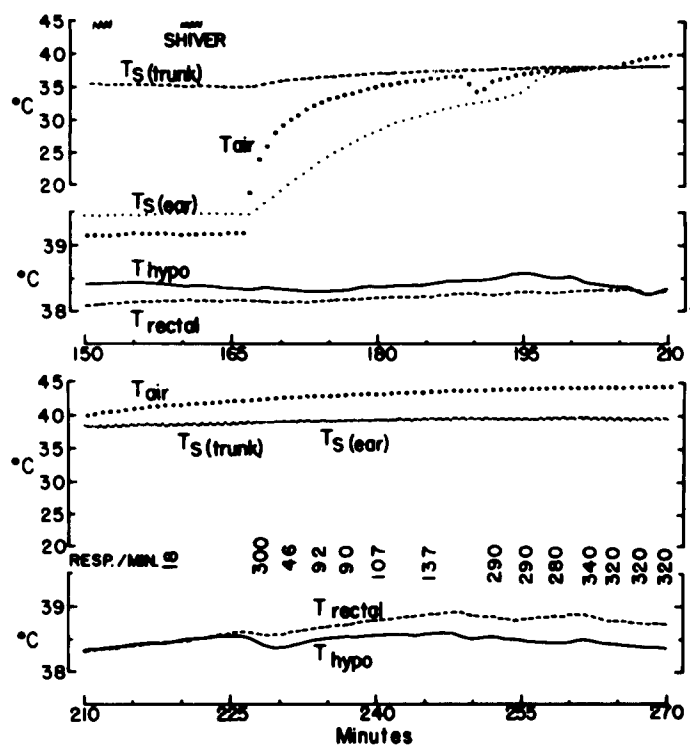

Fig. 4b Body temperatures of same dog as Fig. 3 resting and fasting exposed to neutral, cold, and hot environments.

Figure 4b is a continuation of Figure 4a. Starting at 167 minutes, the air temperature was increased to 45°C. The hypothalamic temperature passively increased to 38.6°C with no panting. 45 minutes later, the dog was panting vigorously although the hypothalamic temperature was down 0.1°C to 38.5°C. Note, this is no higher than it was when the animal was shivering vigorously; and, also, it is 0.4° to 0.5°C higher than it was in Figure 3 when the same dog was panting no less vigorously and had no higher skin temperature.

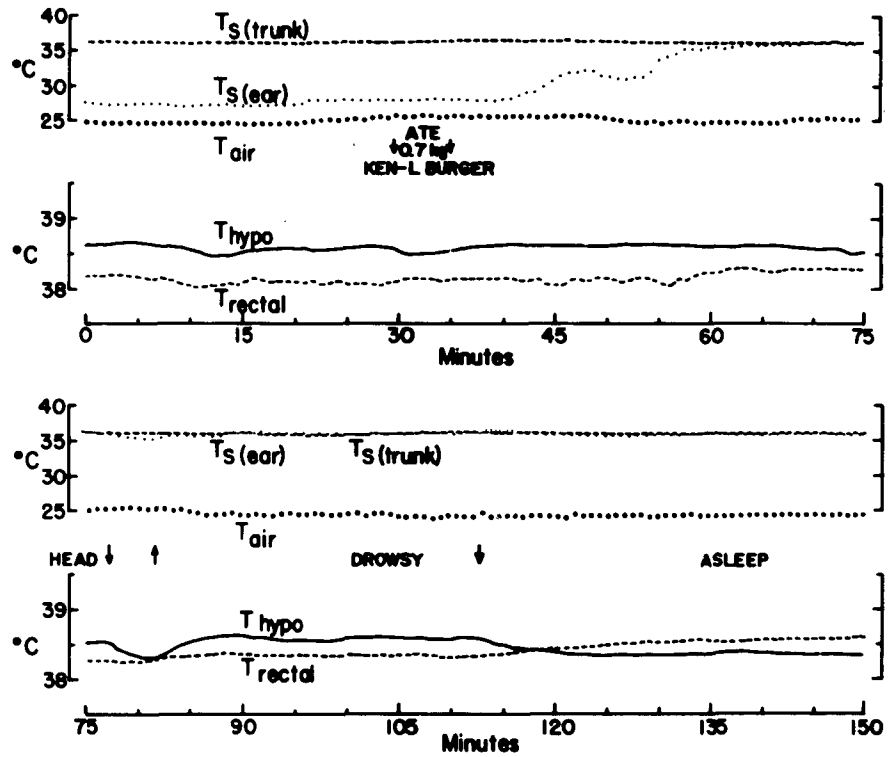

Fig. 5 Body temperatures of same dog as Fig. 3 resting and feeding exposed to neutral environment.

Figure 5 is another record on the dog in an ambient temperature maintained at 25°C throughout the run. After a long, quiet period, the animal was fed 0.7 Kg of Ken-L-Burger. Before feeding, the ear skin temperature was only a few degrees above ambient thus indicating vasoconstriction. Shortly after feeding, the ear skin temperature rose slowly to 36°C due, no doubt, to vasodilation. There was no apparent elevation of the hypothalamic temperature,

following food intake, to account for the vasodilation, since the hypothalamic temperature after feeding was never higher than before feeding when the ear was vasoconstricted. Later, when the animal fell asleep, the hypothalamic temperature fell 0.3°C to 38.35°C and no vasoconstriction occurred.

B. Hypothalamic Temperature of Monkey Exposed 24 Hours to Hot, Neutral, and Cold Environments

The hypothalamic temperature of a rhesus monkey exposed for 24 hours to a hot environment (35°C), neutral environment (30°C), and a cold environment (20°C) is seen in Figure 6. The relative humidity was held to 50% at each temperature. (Note that in Figures 6 and 7, the upper part of each figure runs from noon to midnight and the lower part from midnight to noon.)

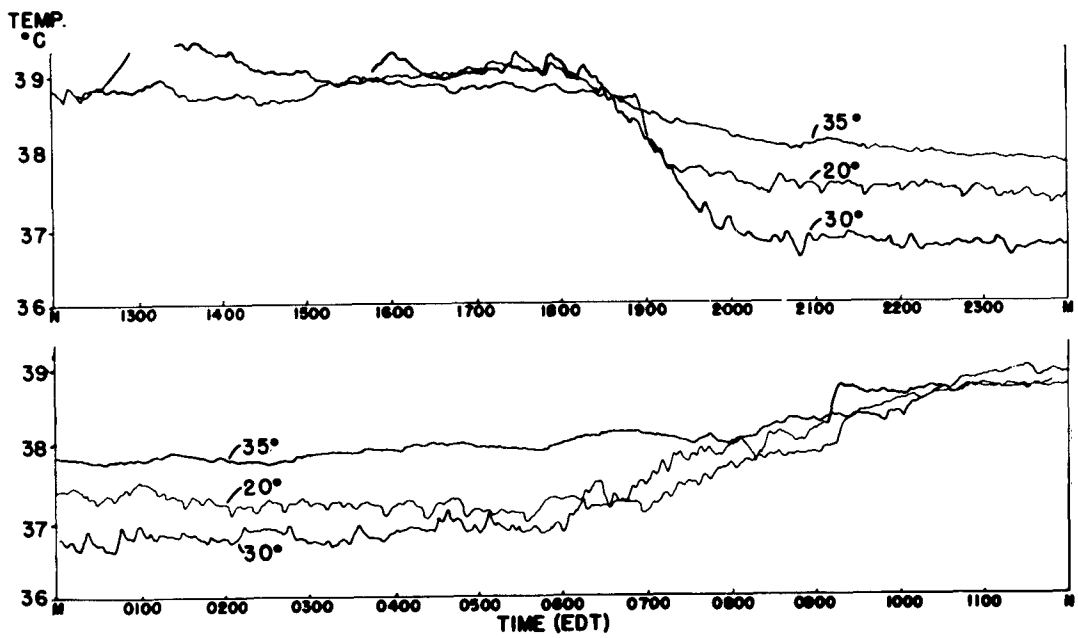

Fig. 6 Hypothalamic temperatures of a rhesus monkey restrained in a primate chair in hot (35°C); Neutral (30°C); and cold (20°C) environments (50% relative humidity) for 24 hour periods with normal day-night lighting.

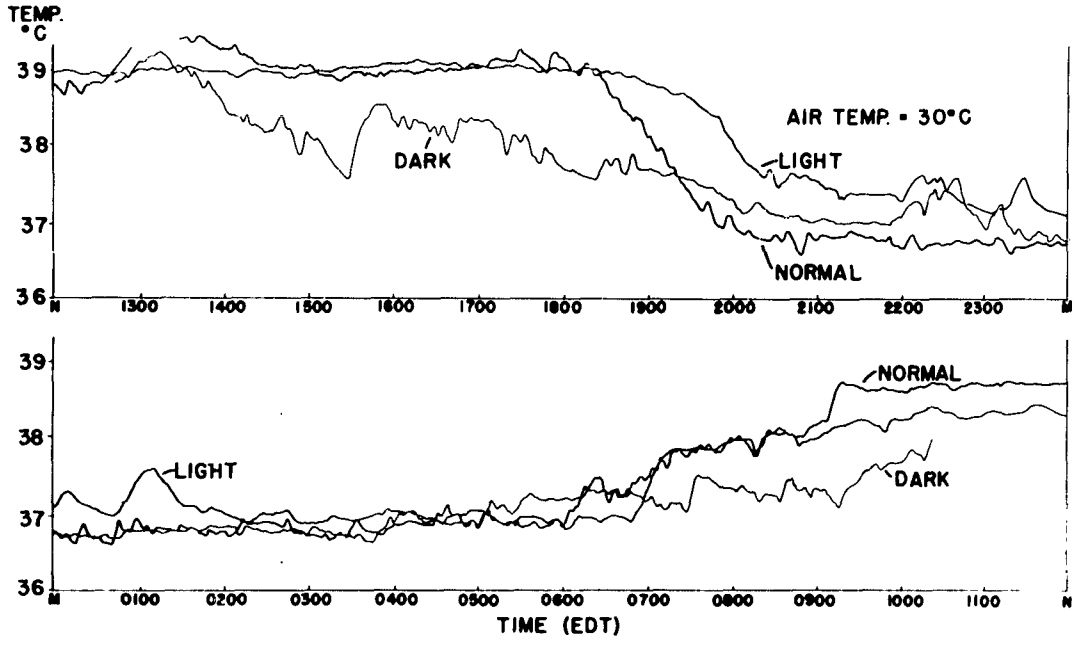

Fig. 7 Hypothalamic temperatures of a rhesus monkey in neutral environment for 24 hour periods with normal day-night lighting, constant light and constant dark.

On each of these three days, the light in the climatic chamber was turned off at 1800 and turned on again at 0900. After 0615, daylight from the laboratory could also enter through a small, uncovered window in the chamber. The monkey had been living in a primate chair for two months, since the time the thermodes were implanted, and was trained to feed itself at will from a food-pellet dispenser. During the hours of light, the hypothalamic temperature was regulated at 39.1° $\pm$ 0.2°C for all environmental temperatures. In each instance, soon after the light was turned out, the hypothalamic temperature fell to another level by an amount depending upon the ambient temperature. In the neutral 30°C environment, the hypothalamic temperature fell within 2 hours to 36.8° $\pm$ 0.2°C and remained so throughout the night. In the hot environment, the hypothalamic temperature fell to only 38.0° $\pm$ 0.1°C and remained so with only small fluctuations throughout the night. In the cold environment (20°C) which produced vigorous shivering day and night, the temperature fell to an intermediate level

of 37.5° ± 0.2°C and stayed so throughout the night. In each instance, the hypothalamic temperature returned to the daytime level more slowly than it fell the evening before. The onset of the rising temperature occurred at about 0600, and the daytime temperature was achieved by about 1000.

As seen in Figure 7, the time the hypothalamic temperature started to change from the daytime level to the night level in a neutral environment was delayed by about one hour in constant light; and the night level was achieved more irregularly and later in constant light. In constant dark, the onset of the night level occurred within two hours after turning the light off at noon, and the temperature fell very irregularly and required nearly 10 hours to come to the night level. Constant darkness also delayed the rise in temperature toward the day level the following day.

C. Thermal and Metabolic Responses of a Resting Dog Exposed to Neutral and Cold Environments with Thermal Clamp on Hypothalamus

In Figure 8a the metabolism of the same dog as in Figure 3 is recorded for 2 hours at 10°C environment. With its hypothalamic temperature maintained

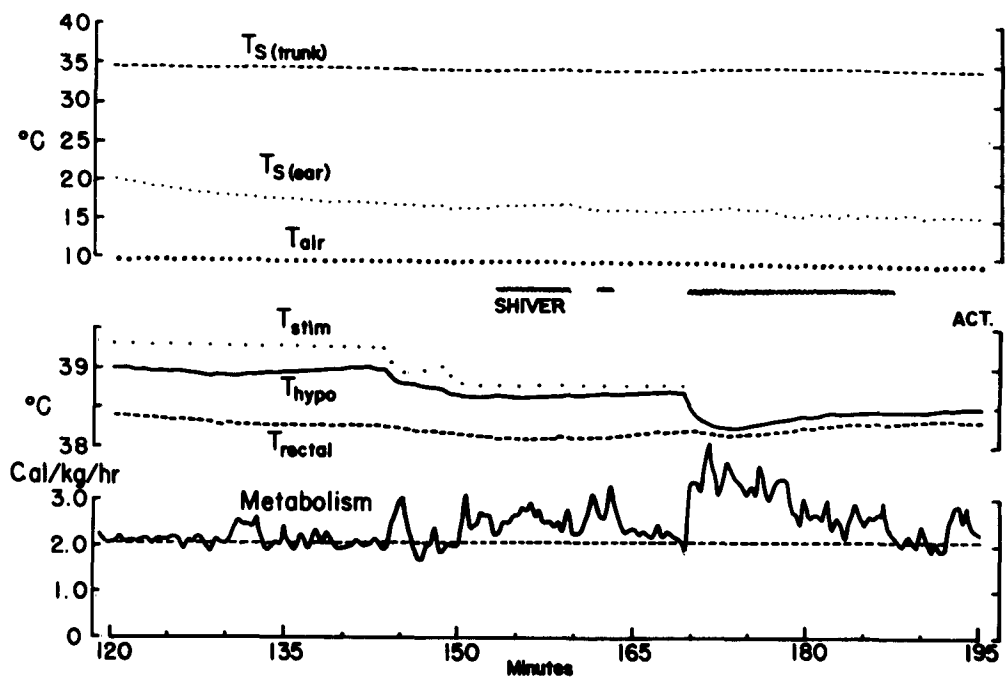

Fig. 8a Body temperatures, heat production and temperature of thermal stimulator for the same resting, fasting dog of Fig. 3 exposed to cold environments.

at about 39°C by perfusing the thermodes with water at 39.3°C, its metabolism was very close to the resting and basal level. At 143 minutes, the hypothalamic temperature was dropped to 38.7°C by dropping the perfusing water to 38.8°C. There was a clear increase in heat production that must be related to the low skin temperature acting upon the hypothalamus which was still above any temperature which would normally be found in the hypothalamus during shivering. At 169 minutes, the "thermal clamp" was removed. The hypothalamus quickly dropped to 38.3°C and shivering and metabolic rate sharply increased.

A 50 percent increase in heat production by vigorous shivering appears to result from a hypothalamic temperature of 38.3°C and low skin temperature although similar temperatures may produce no shivering, as in Figure 4a between 110 and 120 minutes. In Figure 8a the rectal temperature slowly increased to 38.5°C and the metabolic rate declined to the resting level and shivering ceased even though the skin temperature was no higher than during shivering.

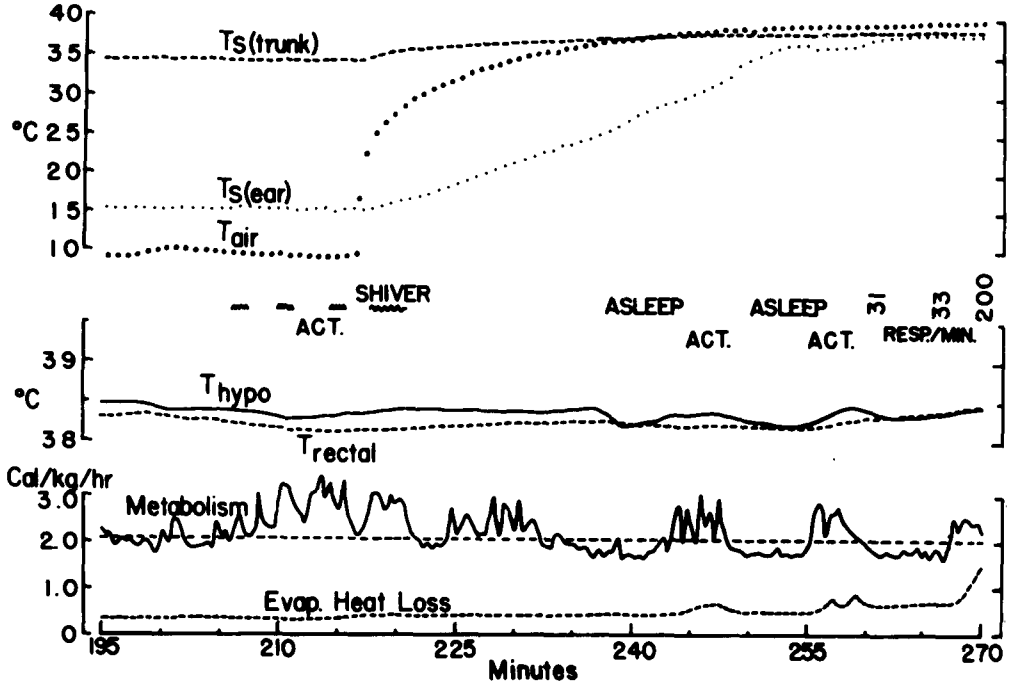

Fig. 8b Body temperatures, heat production, evaporative heat loss from mouth and temperature of thermal stimulator for the same resting, fasting dog of Fig. 3 exposed to cold and hot environments.

Figure 8b is a continuation of the run recorded in Figure 8a. Shivering and restlessness increased the heat production again as the hypothalamic temperature dropped to 38.4°C from 38.5°C. After 216 minutes, the air temperature was increased from 10°C to 40°C. For a 30 minute period, the skin temperatures passively increased and vasodilation probably occurred at about 248 minutes. Vigorous panting, indicated by a respiration rate of 200 and a sharply increased evaporative heat loss, occurred at the end of the run at a hypothalamic temperature of 38.4°C, a temperature at which the dog was shivering (at 218 minutes) while the skin temperatures were still low.

Similar observations on another dog, a short-haired animal, less well acclimatized to cold, are seen in Figure 9. For a full hour, the dog rested quietly in a warm 30°C environment and its metabolism was basal at 1.6 Cal/kg/hr.

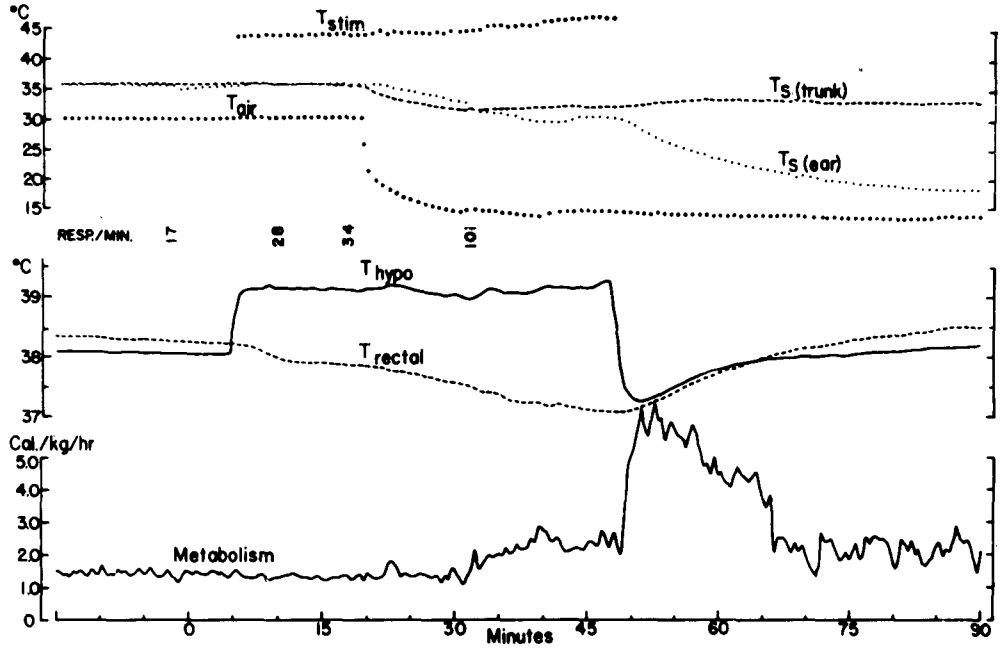

Fig. 9 Body temperatures and heat production of resting, fasting dog with thin fur exposed to neutral and cold environments.

At the time noted, the thermodes were perfused with 44°C water which elevated the hypothalamic temperature to 39.3°C at the point measured. This did not effect the skin temperatures since they were already high. The metabolism was only slightly diminished and respiration rate was doubled so that the rectal temperature started to fall. 15 minutes later, the air temperature was dropped from 30° to 14°C. Although the animal did not appear to vasoconstrict (the ear temperature was held at 30°C), the skin temperatures fell 3° to 5°C and there followed a good 50 percent increase in heat production by shivering. This shivering must have resulted from extra-hypothalamic receptors, from skin receptors or core receptors stimulated by a core temperature of 37.5°C (or lower) acting upon an extraordinarily warm hypothalamus. At 49 minutes the thermal clamp was shut off. The hypothalamic temperature quickly fell to 37.2°C which is about 1°C below normal for the dog and the heat production increased to 4 times basal.

At the same time, the ear vessels vasoconstricted since the skin temperature curve turned sharply downward. As the hypothalamic temperature increased rapidly to above 38°C, the heat production markedly diminished to 25 to 50 percent above the resting level.

DISCUSSION

Regulation of body temperature implies that there is some temperature in the body from which a displacement will elicit an appropriate response either to increase or decrease the body temperature, and the effect of the response will be to reduce the size of the temperature displacement or "load error" but not necessarily reduce it to zero. The reference temperature in any regulated system has been named the "set point." The set point is better understood to be a narrow zone of a width depending upon such factors as the response time of the system, the gain of the unit that activates the effector mechanisms and the type of control involved; i.e., on-off control, proportional control, rate control, or some combination (ref. 7). This concept of regulation of body temperature implies, further, that there is a unique effector response for each set of internal conditions.

Assuming the body temperature is regulated and that there is a unique response for every set of conditions, the results obtained so far indicate that the conditions must include more than skin and hypothalamic temperatures. These results suggest that, at the very least, (1) other core temperatures are involved and/or (2) parameters other than temperature alone are involved which have their influence by adjusting the set point. These parameters may include sleep, wakefulness, feeding, body position, muscular activity, apprehension, etc.

Discussion of the results reported here can best be served by advancing a working hypothesis based on one basic assumption, namely, that there are in the anterior hypothalamus two sets of temperature sensitive neurons both of which increase their activities (firing rate) with increasing temperature. The

only difference between the two sets of neurons is that they have widely different Q_{10}'s relating firing rate to temperature, and the set of sensors having the higher Q_{10} provides facilitation to effector neurons subserving panting, sweating, vasodilation or any heat dissipating response and inhibition to effector neurons subserving shivering and heat conservation. Conversely, the set having the lower Q_{10} provides facilitation to neurons subserving shivering and inhibition to neurons subserving heat dissipation. The Q_{10} of the latter set of sensor neurons may be as low as 1 but need not be less than 1, i.e., need not increase firing rate with decreasing temperature, a response which would be most atypical for biological cells.

Figure 10 is an attempt to illustrate one plausible concept of some of the essential features of the hypothesis.

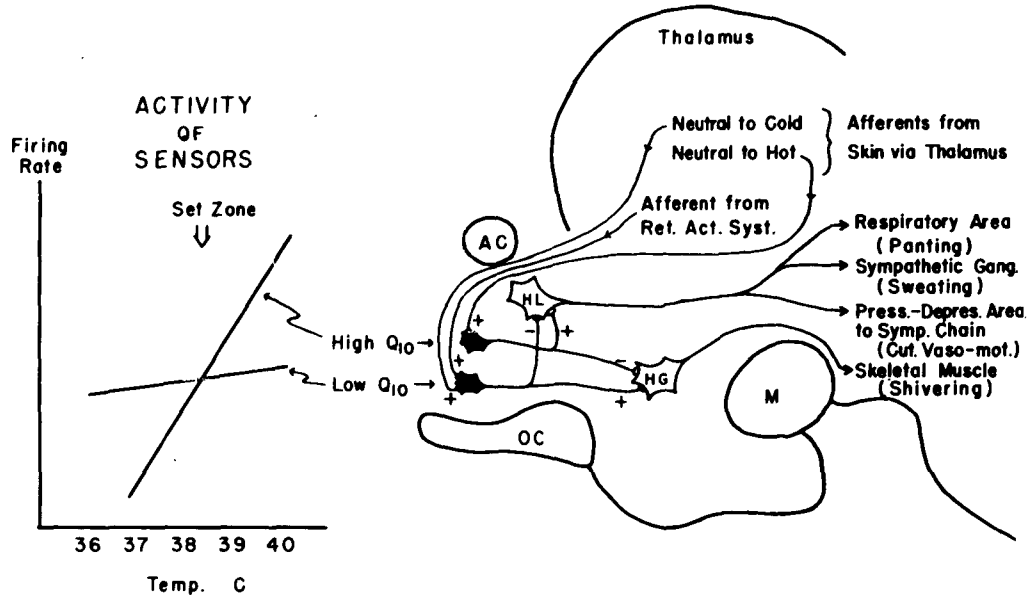

Fig. 10 A physiological model for establishing a set point temperature and illustrating possibilities for adjusting the set point. AC, anterior commissure; OC, optic chiasm; M, mammalary body; HL, a heat loss effector neuron; HG, a heat gain effector neuron; cross hatched cell bodies, low Q_{10} and high Q_{10} sensor neurons.

The two sets of sensor neurons, one labeled "high Q_{10}" and the other "low Q_{10}," are illustrated with cross hatched cell bodies.* Axons of each set must have the capability for both facilitation and inhibition. Whether this capability for facilitation and inhibition is combined in a single unit as shown in Figure 10 or whether it is achieved through two or more neuronal units is not important to the hypothesis as long as there is such a functional capability, as has been described in the spinal cord (ref. 8). The proportion of facilitation to inhibition for each set of sensors is shown to be one-to-one, without any evidence for this at all. The actual proportionality could depend upon, among other things, the spontaneous firing rates of the effector cells as well as upon the function subserved by the effector cell, for example, the proportion of facilitation to inhibition to a heat loss effector subserving panting may differ from that to a heat loss effector subserving vasodilation. Both sets of sensor neurons must have the same anatomical location in order that they be at the same temperature at all times. They are shown here in the anterior hypothalamus (ref. 4) although they may be diffusely distributed in other parts of the hypothalamus. When the temperature of the sensors is within the set zone of temperatures, the firing rates of both sets of neurons are equal so that the facilitation of one set equals the inhibition of the other set and the activity of the common effector neuron is zero. These then are the necessary conditions for establishing a reference temperature for the regulation of body temperature.

However, the results reported above have clearly shown that an animal engaged in normal regulation would exhibit very different responses for the same hypothalamic temperature when exposed to different ambient temperatures or would exhibit the same responses at widely different hypothalamic temperatures at different times depending on whether asleep or awake.

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* The high Q_{10} sensor is shown here as a single neuron. The sensor may, however, consist of several neurons each having a firing rate Q_{10} of about 2 but connected in series so that each neuron facilitates the following neuron in the series. A 10°C increase in temperature would then double the firing rate of the first neuron in the series. The temperature increase would also double the firing rate of the second neuron in the series; but since it is also receiving temperature dependent facilitation from the first neuron, its actual firing rate is more than doubled for the same 10°C increase in temperature. Thus by such a cascade effect, the last neuron in the series may be responding to temperature like the one high Q_{10} sensor depicted in Figure 10. The present hypothesis requires that there be sensors with a high firing rate Q_{10}, but there is a warning to be noted. Suppose that the firing rates of all neurons were temperature dependent. Then any series connection of neurons would render that system highly temperature dependent. Thus, except under specialized conditions where temperature dependence is required, it may be inferred that the firing rates of neurons are not normally temperature dependent ($Q_{10} = 1$) or that there are neurons in the series of neurons which inhibit the following unit in order to temperature compensate for those which facilitate. The same considerations are encountered in any regulated system where a sensor role is allocated to a neuron.

This may be interpreted as indicating that the two sets of sensor neurons must be influenced in such a way so as to adjust the set zone which may occur in at least two ways. The firing rate of each set of sensor neurons may be facilitated or it may be inhibited. In the schema in Figure 10, only facilitation has been indicated and by itself is sufficient. The activity of the sensor neurons may also be effected by anesthesias, endogenous pyrogens, etc., and if the effect on one set is different from the effect on the other, the set zone will be shifted. Three main afferent inflows are illustrated to show the facilitation of the sensor neurons. Afferents from skin receptors which have a low, steady state discharge at neutral skin temperatures and which increase both the phasic and steady state discharge when cooled (ref. 9) are shown to facilitate the set of sensor neurons of low Q_{10}. Likewise, afferents from the reticular activating system of the brain stem which has its upper end in the posterior hypothalamus and lower thalamus are shown in Figure 10 to facilitate the low Q_{10} sensors. Afferents from skin receptors which give a phasic discharge with rising skin temperature and a steady state discharge at very high skin temperatures (above 37°C) (ref. 9) are shown to facilitate the high Q_{10} sensors. At this time, connections between the skin receptors and the hypothalamus as well as connections between the reticular activating system and the hypothalamus have not been demonstrated and may only be considered plausible connections. Afferents from thermal receptors in the core (ref. 4, 10, 11), or in veins draining active muscle (ref. 12) may also facilitate (or inhibit) the sensor neurons; but these have not been illustrated in Figure 10. Other possible facilitory (or inhibitory) afferent connections with the sensor neurons (and possibly also with the effector neurons) from the frontal lobes and the medial forebrain bundle have not been illustrated either.

One other feature of the schema in Figure 10 is the two effector neurons shown in the hypothalamus. The one with the cell body labeled HL is shown subserving (1) panting by axons terminating in the respiratory area of the medulla, (2) sweating (in monkey) by ultimate connections with the sympathetic ganglia, and (3) cutaneous vasomotion via medullary vasomotor areas. For simplicity, a single neuron is shown to subserve three heat loss functions. Each function is more likely achieved by its own set of effector neurons having their own proportion of facilitation and inhibition from the sensor neurons. The other effector neuron with cell body labeled HG is shown to subserve shivering by action upon skeletal muscle neurons. It is not essential that these effector neurons be shown in the hypothalamus. The essential feature is that effector neurons in the chain leading to a regulatory response be facilitated by one set of sensor neurons and inhibited by the other or vice versa. However, heat loss effector neurons may be found in the anterior hypothalamus since electrical stimulation there does elicit panting, etc. (ref. 13). Electrical stimulation of the two sets of sensors simultaneously should lead to equal and opposite effects, with no net response. Similarly electrical stimulation in the posterior hypothalamus produces shivering (ref. 14), therefore a heat gain effector neuron was placed there. Lesions in the rostral hypothalamus render the dog unable to pant and to prevent hyperthermia in a hot environment whereas lesions in the caudal hypothalamus eliminate the shivering response in the dog but leaving intact the ability to pant (ref. 15).

Another possible characteristic of the effector neurons is that their excitability be influenced by blood borne constituents (not illustrated). For example, adrenalin and noradrenalin may increase the excitability of neurons in the effector chain leading to shivering (ref. 16, 17). Modifying the excitability of the effector units would not change the set point of regulation but only the "gain" or responsiveness of the effector mechanism.

The gain of the system is defined as the proportionality constant, a, relating the response to the load error, i.e.

$$\Delta R = a(T_h - T_{s.p.})$$

where the response R may be metabolism, vasomotion, panting, etc., T_h is the actual hypothalamic temperature, $T_{s.p.}$ is the set point or reference temperature and $(T_h - T_{s.p.})$ is the load error. According to the present hypothesis, the gain a is related to the difference in slopes of the activity curves of the low Q_{10} and high Q_{10} sensors. The greater the difference in slopes of the two curves in Figure 10, the greater will be the gain. Like the set point, the difference in slopes of the activity curves may also be dependent upon such physiological factors as skin temperature, core temperature, etc., although the model depicted in Figure 10 does not indicate how this can be achieved.

Four thermoregulatory problems which may be described in terms of the adjustable set point hypothesis outlined in Figure 10 are illustrated in Figure 11.

A. Set points during the day in neutral and cold environments.

Referring to Figure 11-A, the set point of the wakeful dog is shown to be 38.4°C in a neutral environment. This, of course, may vary $\pm$ 0.1°C in the same dog from time to time; and may be somewhat different in another dog, and may be considerably different in a different species; e.g., 39°C in the monkey. Whether the set point varies from time to time by as much as $\pm$ 0.1°C or whether it remains constant and the actual temperature fluctuates about the set temperature is of no matter. The fact is that in a neutral environment the actual hypothalamic temperature does vary by as much as $\pm$ 0.1°C in a wakeful dog and no immediately corresponding thermoregulatory responses are seen. So either the set point is changing by these small amounts or the load error must exceed about 0.1°C before a response is elicited.

In the neutral environment, the facilitation of the low Q_{10} sensors by afferents from cutaneous receptors is shown to be low. When the animal is transferred to a cold environment, the steady state discharge and possibly some phasic discharge from the cutaneous cold receptors is shown to increase the facilitation of the low Q_{10} sensors, thus raising the set point. If the hypothalamic

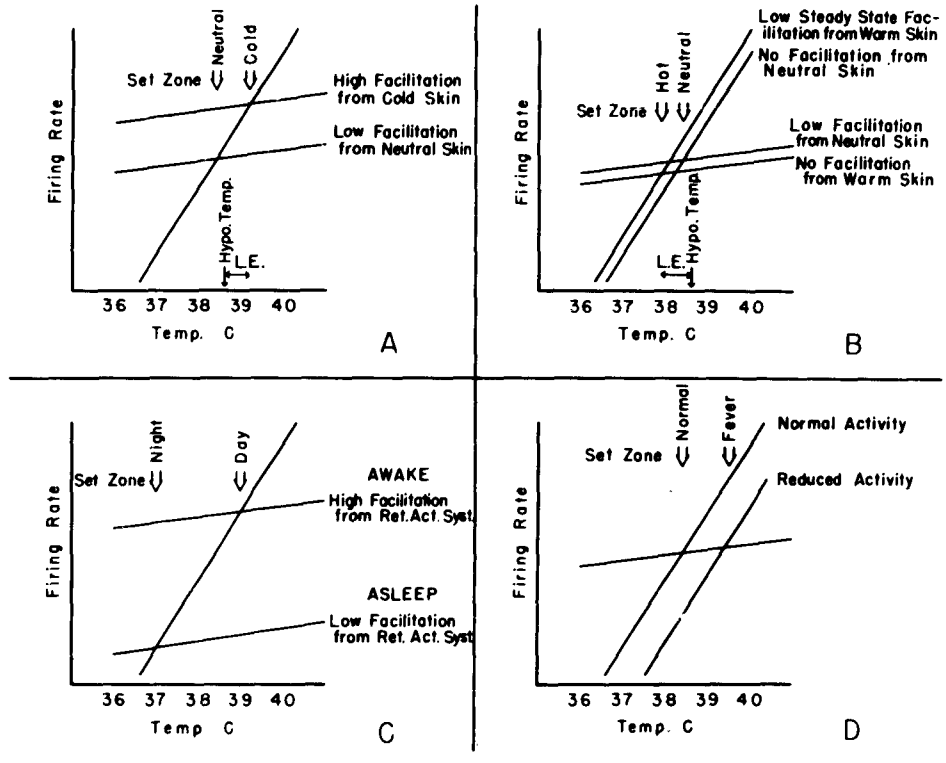


Fig. 11 Hypothetical relationships illustrating how the adjustable set point theory can describe temperature regulation in A-neutral and cold environments; B-neutral and hot environments; C-waking and sleeping states in neutral environment; and D-normal and fever states.

temperature remains the same as in the neutral environment, or even if it increases a little it will still be below the set point and the load error will drive shivering. The seeming paradox is that whereas the hypothalamic temperature may be higher in the cold environment than it was in the neutral environment, nevertheless that hypothalamic temperature is driving shivering; and certainly if the hypothalamic temperature were lowered by local cooling, shivering would increase and if it were raised by local warming, shivering would diminish.

B. Set points during the day in neutral and hot environments.

If the wakeful animal is transferred to a hot environment, then two changes are depicted in Figure 11-B. The low facilitation of the low Q_{10} sensors coming from the low steady state discharge from the neutral-cold receptors of the neutral skin is reduced to zero as the skin temperature increases. Second, there is shown to be some facilitation of the high Q_{10} sensors by afferents from cutaneous warm receptors which yield a steady state discharge if the skin temperature is high enough and a phasic discharge at lower but rising skin temperatures. The combined effect of these changes is to lower the set point in the hot environment. If now the hypothalamic temperature increases a little or even if it doesn't, it would then be above the new set point and drive the heat dissipating mechanisms by an amount which would prevent further increase. Again, local heating of the hypothalamus would produce increased panting in the dog and local cooling would yield less panting.

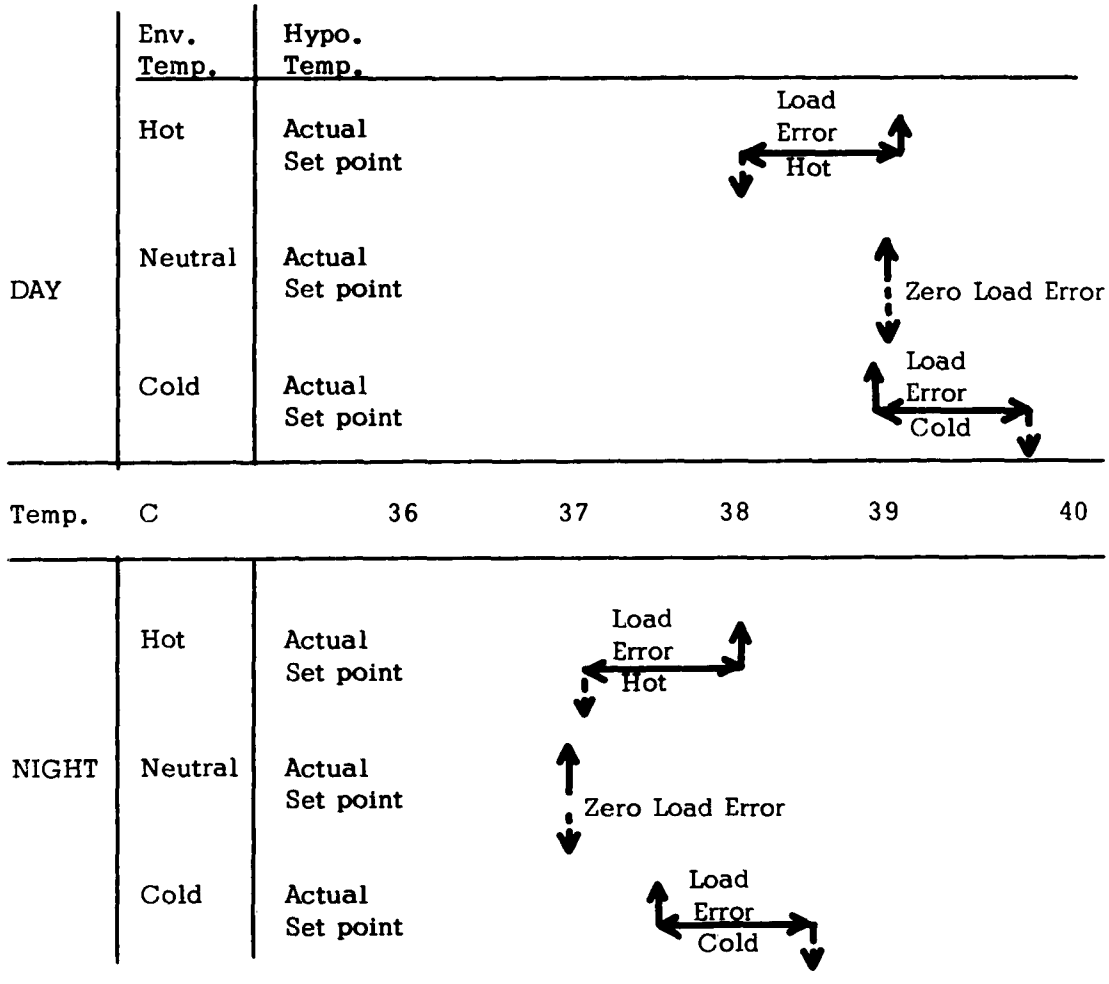
C. Sleep-Awake set points in neutral environment.

During waking hours facilitation of the low Q_{10} sensors by the reticular activating system (RAS) increases their firing rate (according to the present hypothesis) and elevates the set point temperature to about 39.0°C in the monkey and 38.4°C in the dog in a neutral environment. When the animal becomes drowsy, the RAS facilitatory effect is reduced, and decreases to a low level in deep sleep. Thus when the dog is drowsy or enters light sleep, a drop in hypothalamic temperature of 0.3° to 0.5°C in 5 minutes due to any cause; e.g., increased hypothalamic blood flow, does not elicit shivering. In fact, if the hypothalamic temperature did not fall abruptly for some reason and if the cutaneous arterioles were not already dilated in a neutral environment, then they should dilate and the ear temperature should rise quickly when the animal did enter light sleep since the prevailing hypothalamic temperature would be above the now lowered set point and a load error would exist which should drive vasodilation.

The hypothalamic temperature of the dog during the night was found to be below 37.0°C when the animal was presumably asleep. Similarly for the monkey, when the light was turned off at 1800 the hypothalamic temperature fell in two hours from the daytime temperature of about 39.0°C to below 37.0°C and remained so throughout the night in a neutral environment. A similar observation has also been made by C. Hamilton (personal communication). The diagram in Figure 11-C suggests that when the monkey fell asleep, facilitation of the low Q_{10} sensors by the RAS was reduced to a low level causing the set point to be dropped by 2°C. If the monkey were exposed to a cold environment during the night, the RAS facilitation would probably be greater than in the neutral environment, and there would be an additional facilitation by afferents from the skin receptors so that the set point would be something over 37.5°C, say 38.0°C; thus the difference between

the actual hypothalamic temperature, 37.5°C, and the set point temperature might give a load error sufficient to drive the shivering. In the hot environment, the set point again fell due to reduced facilitation by the RAS and from the neutral to cold skin receptors. The set point was reduced enough so that the actual hypothalamic temperature of 38.5°C gave sufficient load error to drive the heat loss mechanisms.

The regulation of the hypothalamic temperature of the monkey in the daytime in hot, neutral, and cold environments may best be reconciled with the hypothesis presented above by referring to the following chart.



In the day in neutral environment the set temperature is shown to be 39.0°C and the actual temperature is about the same; that is, zero load error and no regulating responses. In the hot environment, the set point would be lowered as described in B above. Only a slight (or no) increase in hypothalamic temperature would suffice to produce a load error sufficient to drive heat loss mechanisms to maintain the hypothalamic temperature constant throughout the day. In the cold environment, the set point would be increased as described in A above so that if the hypothalamic temperature remains the same or even increases a little there is sufficient load error to drive shivering and prevent a fall in hypothalamic temperature.

For comparison, the actual and set point temperatures during the night are also shown. In the neutral environment the set point has dropped 2°C from what it was during the day, but so also has the actual hypothalamic temperature and there is zero load error. In the hot environment, the decrease in the set point during the night was not so great as in the neutral environment due perhaps to a greater difficulty in sleeping in the heat, i.e., a greater afferent input to the RAS. Nevertheless, the set point was about the same as in neutral environment because it was also lowered by increased facilitation of high Q_{10} sensors and decreased facilitation of low Q_{10} sensors (B above). The actual temperature was above the set point by the load error sufficient to produce an amount of heat loss to maintain a constant temperature of about 38.0°C. Note that the day and night load errors in the hot environment are shown to be about the same. In the cold environment, sleep was again more difficult so that the facilitation provided by the RAS did not decrease as much as in the neutral environment. Also there was increased facilitation from the cold skin receptors so that the set point was high. The actual hypothalamic temperature was 37.5°C during the cold night or enough below the set point so that the load error would drive enough shivering to maintain a constant hypothalamic temperature. The load error in the cold at night was chosen to be about the same as the load error in the cold during the day.

There is, in sleep, a reduction of metabolic rate which might suggest an alteration of the present hypothesis. The metabolic rate in man, during sleep, may be as much as 10-15 percent below the BMR and is certainly less at night than during the day when active. The same must also be true of a monkey even when restrained in a primate chair. This might suggest that the set point is not lowered with the onset of sleep in a neutral (30°C) environment, but that by some means the gain of the regulatory mechanism is reduced. Since the metabolism is reduced in sleep, the heat loss will at first exceed heat production and the hypothalamic temperature will fall with the core temperature. The core and skin temperatures will fall to such a level that the heat loss from the core to the skin and from the skin to the environment equal the lower night level of heat production. A fall of skin temperature of ΔT_s which reduces heat loss from the skin to the 30°C environment at night must be accompanied by either a decrease in the conductance of body tissue through increased vasoconstriction or by a fall in core temperature equal to $(1+\frac{K_f}{K_t})\Delta T_s$ where K_f is the conductance of the fur and air

from the skin to the environment and K_t is the tissue conductance ($\frac{K_f}{K_t} \simeq 1/2$). The supposition was that the set point was not lowered with the onset of sleep and the effector responsiveness was reduced in order to prevent shivering with a fall of 2°C in the hypothalamic temperature. The reduced effector responsiveness would also very likely reduce vasomotion so that the monkey would not vasoconstrict and might even vasodilate. The consequence of a reduced metabolism at night would then be a passive fall in core temperature equal to or more than 1-1/2 times a passive fall in skin temperature. This description is just barely plausible in a neutral 30°C environment, but in a hot (35°C) environment a reduced gain at night would predict that the hypothalamic and core temperatures would passively increase to a level above the day temperatures whereas, in fact, the hypothalamic temperature is 1°C lower at night than in the day in the 35°C environment. Therefore, it appears that the observations of the hypothalamic temperatures in the monkey may be better described by a set point shift at constant gain rather than by assuming that the set point is unchanged with the onset of sleep and only the gain of the thermoregulatory mechanism is reduced. Of course, it is possible that both set point and gain are reduced in sleep.

A drop in the set point temperature in sleep would account for a number of interesting thermoregulatory phenomena associated with going to sleep. Only two will be mentioned here. A rapid fall in the rectal temperature of 1°C or more during the first hour or two of sleep in both Europeans and primitive men has often been observed in studies on cold acclimation while exposing them to moderate cold at night (ref. 18, 19). The falling rectal temperature is often accompanied by a rapidly rising foot temperature. In warm environments, the rectal temperature of both European and primitive men also fell rapidly during the first hour of the night and was always accompanied by a very fast rising foot temperature and average skin temperature. In studies on sweat rate of resting men in hot environments, sweating was often noticed to increase when the subject became drowsy and fell asleep (ref. 20).

The experimental evidence for suggesting that there is a reduction of the set point temperature associated with sleep may be convincing. There is, however, no experimental evidence for suggesting that the reduced set point is achieved by a reduced facilitation of the low Q_{10} sensors by the reticular activating system. The set point shift associated with sleep may also be achieved through changes in pH, osmolarity, glucose level, etc. of the blood perfusing the hypothalamus or, at least, the set point may be effected by such changes in the blood. A neural mechanism for a facilitory role upon the sensors was chosen simply because of the apparent speed of the set point shift. It appears to occur almost instantaneously with sleep. Only because the reticular activating system is much involved in sleep-wake patterns was it suggested for a facilitory role in temperature regulation in the wakeful state (ref. 15). Whether its functional connections with the hypothalamus are direct or indirect cannot be stated.

A close look at Figure 11-C will suggest that if the facilitation of the low Q_{10} sensors is sufficiently small so that the activity of these sensors approaches zero, then below about 36°C temperature regulation can no longer occur. Perhaps it is too much to suggest that this is what occurs at the onset of hibernation. It is certainly true that hibernation always starts when the animal is asleep. Thus, unusually low facilitation from the reticular activating system, possibly accompanied by or perhaps caused by some changes in blood composition may initiate the state of hibernation. Arousal may occur by any event which reactivates the reticular activating system so that the low Q_{10} sensors are again facilitated and these in turn facilitate shivering in the absence of any inhibition from the high Q_{10} sensors.

In hypothermia in man, it is well known that temperature regulation no longer occurs at body temperatures below about 32°-34°C in the absence of any anesthetic. This may be explained by suggesting that anesthesia is required only to reduce the activity of the high Q_{10} sensors and to reduce the facilitation of the low Q_{10} sensors until the hypothalamic temperature has fallen below the temperature (34°-36°C) at which the high Q_{10} and low Q_{10} sensors can no longer establish a set point when the anesthesia wears off. Here it must be assumed that the RAS of the patient, unlike that of the hibernator in normal hibernation cannot be activated by external stimuli, otherwise facilitation of the low Q_{10} sensors would occur and shivering would result. On the other hand, if a barbiturate anesthesia lightens in an animal at normal body temperature, then shivering does occur, suggesting that facilitation of the low Q_{10} sensors occurs before the normal activity of the high Q_{10} sensors is restored as the anesthesia lightens.

D. Set points in normal and fevered states.

By a simple assumption, the elevation of body temperature in fever may be explained. As shown in Figure 11-D, the endogenous pyrogen may act by depressing the activity of the high Q_{10} sensors, thus raising the set point. Regulation would now be in all ways normal except in one; namely, the hypothalamic temperature would be elevated by the amount of the fever in all instances. Heating the hypothalamus will produce panting and cooling will produce shivering. Or if during the chill phase, the hypothalamus is heated, no fever develops until the local heating is terminated. Similarly, if the hypothalamus is locally cooled during the chill phase, a hyper fever is produced so that when cooling stops the dog pants to restore the hypothalamic temperature to the fever level (ref. 21). In unpublished results on the dog alternating rest with exercise, a saw toothed pattern of the rectal temperature of the normal dog was produced as the temperature rose during exercise and fell during rest. This pattern was in all respects the same in the same dog with a Pyromen fever except that the pattern was elevated by the amount of the fever. Similar observations have been published for man (ref. 22).

Some experimental confirmation of some aspects of the adjustable set point hypothesis may be derived from studies of single unit activities in the anterior hypothalamus of the anesthetized (urethanized) cat during local hypothalamic heating and cooling. Only two kinds of units have been described. One type gave little or no increase in firing rate with increasing temperature from well below normal brain temperature to well above (ref. 23), and another group in which the firing rate increased markedly with increasing temperature, with firing rate Q_{10}'s as high as 8 to 10 (ref. 24). Although these results suggest support for the hypothesis advanced, they cannot be considered entirely confirmatory either, for two reasons. The cats were under sufficient anesthesia to immobilize them so that their heads could be held in a stereotaxic instrument; i.e., surgical anesthesia with urethane, and, secondly there are a great variety of neurons in the anterior hypothalamus performing a great variety of functions and only a few percent may be involved in temperature regulation, and of these latter some may be sensory and some may be effector which would indirectly be responsive to temperature changes. Furthermore, any exploration of brain stem for units having temperature regulatory functions, must be made with the realization that somewhere in the chain of neurons leading to shivering there will be units displaying increased firing rates when the sensors driving them are cooled; and, similarly, in the panting chain there may be units which increase activity not because they are heated, but because the sensors driving them are heated. Therefore, the task of sorting out the sensory from the effector units involved in temperature regulation in an unanesthetized animal during thermal stimulation might be extraordinarily difficult.

One last bit of information may be extracted from the results reported here. The inference throughout the discussion has been that the controller of temperature functions by and large by proportional control, that is, the response is proportional to the load error (difference between actual and set point temperatures). This may not always be so, as has been pointed out before where instances of discontinuous response are clearly in evidence in the normal dog (ref. 25). Shivering and perhaps also panting may be voluntarily interrupted for brief periods. Whether sweating and vasodilation may be effected by conscious effort is uncertain. The basis for such on-off control cannot be stated, but it may be achieved through facilitory-inhibitory pathways from the frontal area or other cortical areas again acting upon either the sensor neurons in anterior hypothalamus or possibly directly upon effector neurons. There does seem to be some evidence that there is no phasic response of the central receptors at least during rapid cooling of the hypothalamus of a resting, wakeful dog. For instance at time 50 minutes in Figure 9, there is an enormous rate of fall of the hypothalamic temperature which of itself has no effect on shivering (oxygen consumption). The large increase in oxygen consumption seems to be related only to the low but no longer falling hypothalamic temperature.

The dominant role of extra-hypothalamic core receptors in establishing the set point may also be inferred from Figure 9, under at least one set of conditions. Assuming that the shivering metabolism is proportional to the load error, that is to say,

$$\Delta \text{Met.} = a\,(T_{set} - T_{hypo})$$

where Δ Met. = the rate of heat production by shivering, then an approximate value for the proportionality constant, α, may be calculated by comparing the shivering metabolism immediately before removal of the thermal clamp, at time 49 minutes, with the shivering metabolism immediately afterward. The hypothalamic temperature was approximately 39.1°C before removal of the clamp and it was 37.2°C after removal whereas there was very little change in the rectal and skin temperatures. Solution of the two equations relating shivering and hypothalamic temperature immediately before and after clamp removal without change in rectal, skin, or set point temperatures yields

$$\alpha = 2.0 \text{ Kcal/Kg/hr/°C}$$
$$\text{and } T_{set} = 39.6°C$$

With an approximate value for α, the set point temperature was calculated for each 5 minute interval throughout the experiment of Figure 9 and plotted against the rectal temperature and against the skin temperature ($0.85\,T_{trunk} + 0.15\,T_{ear}$) in Figure 12. It appears that the set point temperature correlates better with the rectal temperature than with the skin temperature. This suggests that in this experiment, at least, the set point was more dependent upon the rectal temperature than upon the skin temperature.

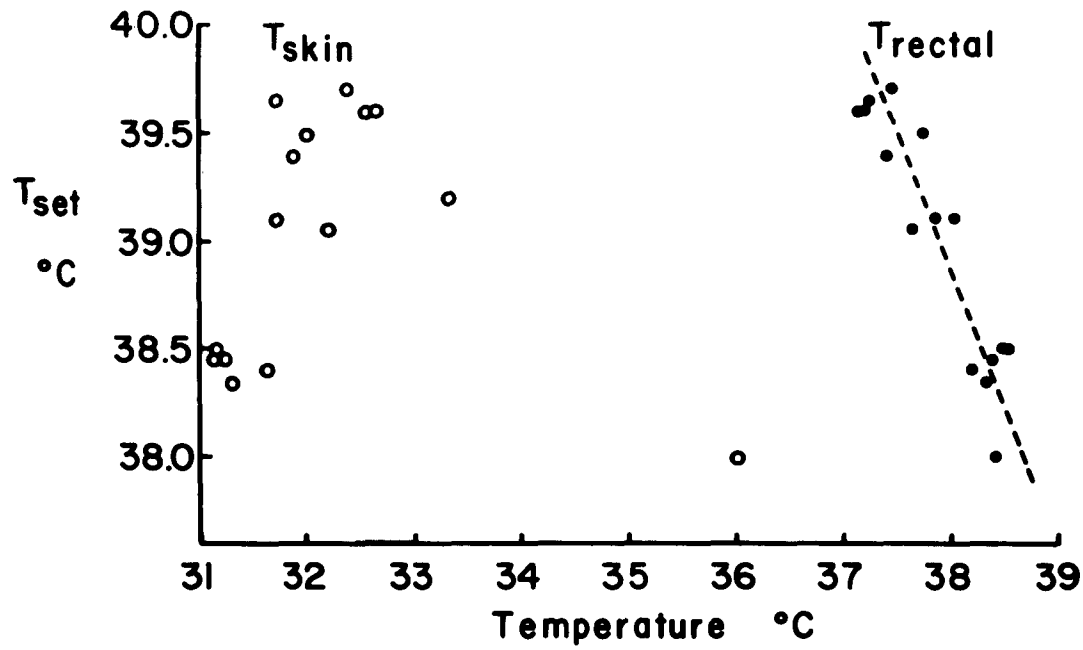


Fig. 12 Calculated values of the set point temperature in Figure 9 plotted against rectal temperature and against skin temperature.

The case for proportional control is strongly supported by the work of Benzinger (ref. 26) on resting man (notwithstanding the major difficulties in equating tympanic membrane temperature with hypothalamic temperature) if at the same time it is understood that facilitation from the phasic and steady state discharge of warm and cold cutaneous receptors, from extra hypothalamic core receptors, and from other sources such as the reticular activating system, cortex, etc. may adjust the set point of temperature regulation. Although the present hypothesis cannot find confirmation in the carefully executed steady state data from Benzinger's laboratory, it does describe and would predict the relationships between heat production and internal cranial and skin temperatures which he has found. It also predicts that the evaporative heat loss is driven by the hypothalamic temperature just as shivering was driven by hypothalamic temperature but with less effect from the skin than was predicted for shivering because sweating in man may prevent a steady state rise in skin temperature which in turn would produce no effect on the set point. A phasic rise in skin temperature on the other hand does affect the sweat rate (ref. 20) perhaps by the mechanism already described.

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Aerospace Medical Division
6570th Aerospace Medical Research Laboratories, Wright-Patterson AFB, Ohio
Rpt. No. AMRL-TDR-63-5. HYPOTHALAMIC TEMPERATURES IN DOG AND MONKEY AND THERMOREGULATORY RESPONSES TO ENVIRONMENTAL FACTORS. Final Report, Jan 63, iv + 30 pp incl. illus., tables, 26 refs. Unclassified report

The role of the hypothalamic and skin temperatures in controlling the thermal response of a resting animal was studied by measurements of (1) hypothalamic, rectal, ear skin and trunk skin temperatures on the resting dog and rhesus monkey (hypothalamic temperature only) in hot, neutral and cold environments; and (2) the thermal and metabolic response of a dog while holding hypothalamus at approximately

(over)

38.7° C by means of six thermodes surrounding the hypothalamus and perfused with water. The results indicate that the parameters involved in temperature regulation must include more than skin and hypothalamic temperatures since an animal engaged in normal regulation would exhibit very different responses for the same hypothalamic temperature when exposed to different ambient temperatures or would exhibit the same responses at widely different hypothalamic temperatures at different times, depending on whether asleep or awake. The discussion of these results includes a hypothesis of a dependent set point which suggests that the set point for temperature regulation depends upon the skin temperature, extra-hypothalamic core temperatures, whether the animal is asleep or awake, and other factors.

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6570th Aerospace Medical Research Laboratories, Wright-Patterson AFB, Ohio
Rpt. No. AMRL-TDR-63-5. HYPOTHALAMIC TEMPERATURES IN DOG AND MONKEY AND THERMOREGULATORY RESPONSES TO ENVIRONMENTAL FACTORS. Final Report, Jan 63, iv + 30 pp incl. illus., tables, 26 refs. Unclassified report

The role of the hypothalamic and skin temperatures in controlling the thermal response of a resting animal was studied by measurements of (1) hypothalamic, rectal, ear skin and trunk skin temperatures on the resting dog and rhesus monkey (hypothalamic temperature only) in hot, neutral and cold environments; and (2) the thermal and metabolic response of a dog while holding hypothalamus at approximately

(over)

38.7° C by means of six thermodes surrounding the hypothalamus and perfused with water. The results indicate that the parameters involved in temperature regulation must include more than skin and hypothalamic temperatures since an animal engaged in normal regulation would exhibit very different responses for the same hypothalamic temperature when exposed to different ambient temperatures or would exhibit the same responses at widely different hypothalamic temperatures at different times, depending on whether asleep or awake. The discussion of these results includes a hypothesis of a dependent set point which suggests that the set point for temperature regulation depends upon the skin temperature, extra-hypothalamic core temperatures, whether the animal is asleep or awake, and other factors.

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1. Temperature regulation (physiology)
2. Environmental Physiology
3. Thermal Stress

I. AFSC Project 7222, Task 722204
II. Biomedical Laboratory
III. Contract AF 33(657)-7603
IV. John B. Pierce Foundation of Connecticut, Inc., New Haven, Connecticut

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V. H. T. Hammel, D. C. Jackson, J. A. Stolwijk, J. D. Hardy
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